E3

deoxynucleosides; wherein at least one of said contiguous phosphodiester-linked 2' deoxynucleosides is unmodified.

E4

- - 50. (Amended) A compound containing an endo- and exonuclease resistant sequence which consists of 2 or 3 contiguous phosphodiester-linked 2'- deoxynucleosides; wherein at least one of said contiguous phosphodiester-linked 2' deoxynucleosides is unmodified. --

REMARKS

The claims are 1-51. Claims 1, 21, 42 and 50 are amended to more particularly and distinctly claim Applicants' invention. No claim has been cancelled or added.

Amendment of the specification to reflect the status of the co-pending application to which Applicants' claim priority is respectfully requested. Applicants thank the Examiner for pointing out this omission.

Independent claims 1, 21, 42, and 50 have been amended to recite that in the claimed modified nucleotide compound, method of inhibiting the function of an RNA, compound containing at least one exonuclease and endonuclease resistant component, and compound containing an endo- and exonuclease resistant sequence, at least one phosphodiester-linked 2'-

deoxynucleoside is unmodified. Disclosure of this characteristic appears throughout the specification, including the Examples. Accordingly, no new matter has been added by the claim amendments.

Claims 1, 2, 4, 8, 12-14, 19, and 42-50 stand rejected under 35 U.S.C. § 102 (b) as being anticipated by Miller (*Biochimie*, 1985). It is said that Miller discloses methyl phosphonate linked oligonucleotides used in antisense inhibition which are encompassed by the rejected claims.

Claims 1-4, 12-14 and 42-50 stand rejected under 35 U.S.C. § 102 (b) as being anticipated by Stein. It is said that Stein discloses phosphorothioate and phosphodiester linked oligonucleotides for antisense usage.

Claims 1-51 stand rejected under 35 U.S.C. § 103 (b) as being unpatentable over Walder in view of Miller (U.S. Patent No. 4,469,863) and Inoue. It is said that Walder discloses that the most important element in the efficacy of antisense oligomers is that they not only retain normal hybridization properties to form RNA-DNA duplexes but also should form substrates that are recognized and cleaved by RNase H. Miller is said to disclose antisense oligomers with all methylphosphonate linkages which are resistant to nucleases and can form stable duplexes with complimentary mRNA. Inoue is said to disclose that as little as three contiguous phosphodiester

linkages flanked by modified nucleotides are capable of forming RNase H - sensitive substrates.

To the Examiner, one of the ordinary skill would have found the claimed nucleotide compounds obvious in view of the three references because of the necessity to reduce the number of methylphosphonate bonds in the oligonucleotide in order to make the RNA-DNA duplex sensitive to RNase which Walder emphasizes as being critical to the efficacy of antisense inhibition. The claimed methods of antisense inhibition and identification are considered obvious for the same reasons.

Miller (*Biochimie*, 1985) discloses oligodeoxyribonucleoside methylphosphonates in which ALL of the normal charged phosphodiester linkages are replaced with nonionic 3'-5' methylphosphonate linkages. These fully modified oligomers are described as being resistant to nuclease hydrolysis and can form stable hydrogen-bonded complexes with complimentary nucleotide sequences such as mRNA.

However, Miller neither discloses nor suggests not fully modifying the phosphodiester linkages or that, by not fully modifying, the resultant nucleotide compound is capable of forming RNase H-sensitive hybrids. Such is the invention of the Applicants.

Miller does not even consider that degradation of RNA may be undertaken. Miller specifically teaches fully modifying the oligonucleotide to protect it from nucleases. It is silent as to RNase H-sensitivity and provides no instruction or guidance as to how a nuclease resistant nucleotide might also be RNA destroying in forming RNase H-sensitive hybrids. There is no suggestion or other motivation in Miller that anything but full modification should be implemented for its oligodeoxyribonucleoside methylphosphonate compounds.

Therefore, it is respectfully submitted that Miller (*Biochimie*, 1985) neither discloses, suggests or otherwise renders unpatentable Applicants' presently claimed invention.

Stein reports on the synthesis, melting temperature and nuclease susceptibility of a series of phosphorothioate oligodeoxynucleotides analogs, either all PS or end-capped with several PS groups at both 3' and 5' ends. Stein also reports on the RNase-H activity of duplexes of poly-rA with S-dT_{40} (all PS) and normal O-dT_{40}. There is no report on the RNase-H activity of duplexes with end-capped oligodeoxynucleotides.

Stein considers that the reduced melting temperatures of duplexes of the phosphorothioate modified oligomers and/or a break in the RNA opposite an S accounts for the increase RNase-H sensitivity. All PS oligomers had the greatest reduction in melting temperature and S-capped

oligomers had melting temperatures closer to normal, all oxygenated, oligomers. Thus, by Stein's teaching, one skilled in the art is directed to use all PS oligomers if increased RNase-H activity is desired, and not to use S-capped oligomers or other non-fully modified oligomers.

Thus, it is respectfully submitted that Stein actually is a teaching away from Applicants' invention and neither teaches, suggests nor otherwise renders unpatentable Applicants' claimed invention.

Walder states that an important element for an effective antisense oligomer is that it be recognized and cleaved by RNase-H. However, Walder does not disclose or suggest that modifying a nucleotide compound, with sufficient spacing between modifications, might yield RNase-H sensitivity.

Miller (U.S. Patent No. 4,469,863) does not cure the deficiency of Walder. Miller is directed to fully modified oligomers and provides no disclosure or suggestion to only partially modify its oligomers, let alone that such would be RNase-H sensitive.

Inoue is concerned with a oligoribodeoxynucleotide probe comprised of a modified RNA sequence attached to a DNA sequence attached to another modified RNA sequence. The

modifications to the RNA sequences is to resist RNase-H -- quite the opposite effect desired by Walder. Further, there is no suggestion or motivation provided by Inoue to modify its probe for use in antisense.

Accordingly, it is respectfully submitted that none of Walder, Miller or Inoue disclose or suggest Applicants' invention; that there is no suggestion or motivation to combine the disclosures of Walder, Miller and/or Inoue; and that, even if combined, the references do not disclose, suggest or otherwise render unpatentable Applicants' claimed invention.

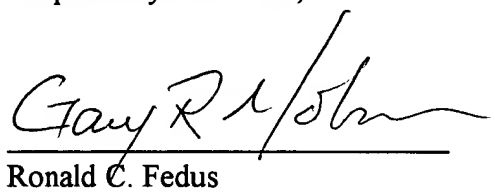
Wherefore, it is respectfully requested that the rejections be reconsidered and withdrawn, and the claims be allowed and passed to issuance.

If it would be helpful in furthering the prosecution of this application, the Examiner is respectfully requested to telephone Applicants' undersigned attorney at the number provided below.

A fee in the amount of $475.00 is deemed due for the three-month extension of time for responding to the Final Office Action (small entity status having been previously established and still being applicable in this application) ands a fee of $395 is deemed due for filing a Submission

Under C.F.R. § 1.129(a) after final rejection. As stated above, authorization is hereby given to charge these fees to Deposit Account No. 05-1135. No other fee is believed necessary in connection with the filing of this Submission. However, if any additional fee(s) is due in connection with the filing of this Submission, authorization is hereby given to charge the amount of such additional fee(s) to Deposit Account No. 05-1135, and to credit any overpayment thereto.

Respectfully submitted,



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